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Tetracaine derivatives for catecholaminergic polymorphic ventricular tachycardia: new drugs for correction of diastolic Ca^{2+} leak?

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Cardiac ryanodine receptors of sarcoplasmic reticulum (RyR2 channels) are major determinants of the magnitude and rate of the cardiac contraction. In adult ventricular myocytes, they amplify small Ca^{2+} signals from sarcolemmal L-type Ca^{2+} channels and provide the majority of Ca^{2+} needed to induce contraction of the myofilaments. In normal physiological conditions, Ca^{2+} release by RyR2 channels occurs only during precise periods of the action potential and is largely absent during diastole. Closure of the RyR2 channels during resting is extremely important not only because it allows refilling of the sarcoplasmic reticulum for the next contracting cycle, but also because the Ca^{2+} that is released during diastole may evoke an untimely action potential: if a critical mass of Ca^{2+} is “leaked” by RyR2 during diastole, it may supercharge the electrogenic sodium-calcium exchanger (NCX) and bring membrane potential to threshold, thus generating triggered activity. The catastrophic consequences of major diastolic Ca^{2+} release have been highlighted by the arrhythmogenic syndrome catecholaminergic polymorphic ventricular tachycardia (CPVT), where excessive Ca^{2+} leak via RyR2 channels destabilized by mutations leads to ventricular fibrillation and other malignant cardiac arrhythmias.

The mechanisms that ensure closure of RyR2 channels during diastole are incompletely understood but an emerging critical player is calmodulin, a protein transducer of Ca^{2+} signals in many cells that binds to and inhibits the activity of RyR2. In ventricular myocytes, a large portion of total calmodulin is presumably interacting with RyR2 channels,¹ perhaps reflecting the key hierarchic role of calmodulin as a stabilizer of the closed state of RyR2. In fact, mutations in calmodulin that hinder its interaction with RyR2 have been linked to

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CPVT^{2,3} and some forms of heart failure with excessive Ca²⁺ leak exhibit calmodulin dissociation from RyR2.⁴

Given the role of diastolic Ca²⁺ leak as generator of cardiac dysrhythmias, it would be desirable to reign in its pernicious effects by designing drugs that selectively stabilize the closed state of RyR2. Interestingly, there is not a single drug in the market specifically prescribed to do this, although some are in clinical trials. β -blockers continue to be the first line of treatment for CPVT despite their incomplete effectiveness to prevent fatal arrhythmic episodes. Carvedilol and its derivatives appear to mitigate arrhythmias in CPVT,⁵ but they decrease the open time of RyR2 and may thus dampen cardiac inotropism substantially. The therapeutic value of flecainide in CPVT mice and patients has been assigned also to its open channel-blockade of RyR2,⁶ but this effect is controversial and it is possible that flecainide prevents arrhythmias mainly by decreasing the threshold for activation of voltage-dependent sodium channels.⁷ Clearly, a fresh approach is needed to fill this therapeutic gap.

In this issue of Heart Rhythm, Klipp et al.⁸ tested a novel derivative of tetracaine, EL20, to prevent arrhythmias in a mouse model of CPVT. The rationale for using tetracaine as the parent molecule of these new drugs is well justified, since tetracaine has long been recognized as a blocker of passive RyR2 Ca²⁺ leak. While other derivatives of tetracaine (i.e., EL9) had already proven efficacious in similar tests, a novel finding in this study is that EL20 blocking effect was calmodulin-dependent: wild-type RyR2 channels that are normally decorated with calmodulin were largely insensitive to EL20, whereas RyR2 channels harboring a CPVT-linked mutation were especially sensitive to EL20. This finding is critical for several reasons. First, it reaffirms the notion, first advanced by Xu et al.,⁹ that CPVT-linked RyR2 mutations induce a conformational state of the channel that promote calmodulin dissociation. While Xu et al.⁹ used a CPVT mouse harboring the RyR2-R2474S mutation, Klipp et al.⁸ inferred a similar mechanism in the RyR2-R176Q mouse, making the pathogenic conformational state more generally applicable. Second, and perhaps more importantly from a therapeutic standpoint, wild type RyR2 channels (supposedly replete with calmodulin) are impervious to EL20 at doses that would otherwise block mutant (and calmodulin-depleted) RyR2 channels. The selective action of drugs on defective targets is a drug designer's dream because it bypasses the often-unavoidable side effects of many medications.

There are, however, a number of considerations to make before hailing EL20 and other tetracaine derivatives as the next generation of antiarrhythmic therapy for CPVT patients. EL20 is after all a derivative of tetracaine, a high-affinity voltage-dependent sodium channel blocker, and as such, some effects on cardiac impulse initiation and conduction could be expected. Although Klipp et al.⁸ assure the reader that no ECG effects were apparent after EL20 administration in CPVT mice, there was no systematic approach to discard this possibility, at least in mice. Flecainide, another high-affinity voltage-dependent sodium channel blocker, *worsens* arrhythmias in structurally-compromised hearts, such as those of heart failure patients, and until now it is only a hope that EL20 may lack significant side effects on structurally normal hearts, such as those of CPVT patients. Second, EL20 appears to selectively correct calmodulin-depleted RyR2 channels, but whether calmodulin depletion is a universal phenomenon in CPVT and other RyR2-induced arrhythmogenic syndromes

remains uncertain, despite the fact that this mechanism has been detected now in two RyR2 mutations. More than 160 RyR2 mutations are currently linked to CPVT, and they lie scattered over a landscape of regulatory domains, Ca²⁺-binding sites, conduction pathways, domain-domain interactions, etc. It is therefore difficult to imagine that all mutations lead to calmodulin depletion, and a patient-specific therapy may have to be designed that depends on the specific pathogenesis of the RyR2 mutation. Coincidentally or not, the two RyR2 mutations so far identified as leading to calmodulin depletion lie in the amino terminal and central part of the channel, respectively, two domains which were known before to naturally interact and “zip” the channel closed.¹⁰ The defective interaction between these two particular domains may be *the* mechanism that promotes calmodulin dissociation, but this only adds to the concern that EL20 may prove ineffective in many other CPVT mutations that do not lead to this particular defective conformational state.

Regardless of the concerns above, the findings of Klipp et al.⁸ should bring new hope to CPVT patients, at least those harboring analogous RyR2 mutations, or others in even different proteins that ultimately evoke similar RyR2 conformational changes. Restoration of calmodulin to other defective channels (L-type Ca²⁺ channels) has attracted attention as a viable therapy for some arrhythmia (long-QT) syndromes, and investigators are opting for adenovirus-mediated delivery of the normal calmodulin gene,¹¹ but many hurdles still lie ahead for this genetic approach. Nothing yet beats the convenience of an orally bioactive, cost affordable pill that is taken in the morning and protects without failure for the rest of the day.

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